DETAILED ACTION

Response to Amendment

1. Applicant's amendment of claims 1, 57, 246, 247 is acknowledged and has been entered.

2. Claims 1, 40, 49-50, 52, 57, 97, 106-107, 109, 246, and 247 are current pending and under examination.

3. Claims 111, 112, 145, 146, 177-180, 182, 183, 215-216 are withdrawn.

Election/Restrictions

4. The election of Applicant's election of the species using a solution having a high ionic strength with traverse in the reply filed on January 26, 2010 is acknowledged. As indicated below, the species was found to be allowable except for the issues under 35 U.S.C. 112, 2nd paragraph, and therefore the search has been expanded to include the non-elected species.

5. The election of species requirement filed December 30, 2009 is thereby withdrawn, and applicant's arguments with respect to the election of species have been considered but are moot.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 40, 49, 50, 52, 57, 97, 107, 109, 246-247 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Regarding claims 1, 57, 246, 247, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). In order to expedite prosecution, for the purposes of examination, the limitation of "using a solution such as a solution having a high ionic strength" is interpreted as "using a solution having a high ionic strength".

9. Claims 1, 57, 246, 247 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the specific type of bonds that attach the second set of molecules to the surface of the second substrate the specific type of bonds between the first and second set of molecules. More specifically, the different species of applying heat, using a solution having high ionic strength, using a solution containing an enzyme, and applying a magnetic field by default are recited to break only the bonds between the first and second set of molecules but not the bonds between the substrate and the second set of molecules, thus requiring the bonds to be different, but the claims do not recite the type of bonds that would allow this condition to occur. Furthermore, the different species appear to break different types of bonds. Therefore, it is unclear what different combinations of bonds would be encompassed by the recited claim, and it would appear that the invention would require these critical elements in order to function properly.

10. The remaining claims are indefinite due to their dependence on an indefinite claim.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1, 49, 50, 52, 57, 106, 107, 109, 246-247 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guire et al. [US 6,514,768] in view of Liang et al. [US 2003/0148304] and in view of Pellicciari et al. [Pellicciari et al., Methods of denaturation and renaturation of DNA in interphasic chromatin: cytochemical quantitative analysis by methyl green staining, 1978, Histochem Journal, 10: pp.213-222] and in light of Miyamoto et al. [US 2002/0015800].

With respect to claim 1, Guire et al. teach providing a master array having a support surface, immobilizing a first set of molecules comprising a plurality of oligonucleotides on the master array support surface to form a pattern of oligonucleotides, hybridizing a second set of molecules comprising multi-ligand conjugates with the oligonucleotides on the master array support surface, providing an assay array support surface, and disassociating the first binding domains from the master array support that permits the conjugates to remain upon the assay support surface, such as by altering the temperature, pH, or salt concentration of the system (column 17, line 40 – column 18, line 25, column 6, lines 16-31), Guire et al. further teach that the multi-ligand conjugates comprise a recognition component comprising an oligonucleotide binding domain selected to bind to the first set of molecules, and a reactive functional group comprising a ligand such as acrylic or vinyl groups in order to bind to an assay array support via attachment sites (column 3, lines 25-45). Guire et al. do not clearly establish that the step of

altering the temperature involves heating, or that the multi-ligand conjugates directly forms a bond with a surface of the second substrate.

Pellicciari et al., however, teaches that DNA in solution is denatured under high temperatures (p.214, lines 3-25). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have altered the temperature in the method of Guire et al. by heating, as suggested by Pellicciari et al., so that the oligonucleotides could be denatured.

Liang et al. further teach a means for immobilizing nucleic acids, and more specifically teach that silane-nucleic acid conjugates can be constructed and reacted with a glass surface at similar efficiencies as normal silane and that this allows for conjugation and glass immobilization reactions to be accomplished in the shortest time, while incurring minimal background signals (para. 0015). Liang et al. further teach that this allows nucleic acids to be attached directly onto untreated glass and silicon surfaces (para. 0004). Furthermore, Miyamoto et al. disclose that bond between the Si in a silane molecule and a glass substrate is strengthened by heating, and therefore, the heating step for breaking the bonds between the DNA molecules would strengthen the bond between the silane and the glass substrate.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have had used functional groups such as thiols as the ligand for immobilizing the multi-ligand conjugates of Guire et al. on the surfaces of assay array supports, which are comprised of glass or silicon, as Liang et al. teach that this would allow for conjugation and glass immobilization reactions of the multi-ligands of Guire et al. to be accomplished in a short amount of time, while producing immobilized ligands that would incur minimal background signals. Furthermore, one of ordinary skill in the art at the time of the invention would have

found it advantageous to utilize the conjugates of Liang et al. as this would allow the conjugates to be immobilized directly on untreated glass or silicon, thus simplifying the method of Guire et al. by avoiding the need for attachment sites.

One of ordinary skill in the art at the time of the invention would also have been motivated to utilize the conjugates of Liang et al., as the application of heat to disassociate the DNA of Guire et al. would strengthen the siloxane bonds between the silane and the substrate. Furthermore since the multi-ligand conjugates of Guire et al. are directed toward immobilization on a support, and since the ligands of Liang et al. are also directed toward immobilization on a support, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in substituting the conjugates of Liang et al. further multi-ligand conjugates of Guire et al.

It is noted that the optional steps recited have not been considered, as they are not recited as being optional for the method and therefore the claims would encompass a method which did not include the steps.

13. With respect to claim 49, Guire et al. teach an embodiment where portions of the second substrate are free of the multi-ligand components (see fig. 1A).

14. With respect to claims 50, 52, Guire et al. teach that the assay arrays may then be used as master arrays to form corresponding assays arrays by the same process (column 18, lines 55-63). Guire et al. teach passivating the surface of the assay array prior to and/or after exposure to the binding partner, such as with a surfactant (column 17, lines 1-5) or using wet chemical etching procedures to etch the substrate (column 21, lines 70-11). Guire et al. further teach washing

excess conjugates from the surface of the substrate (column 21, liens 30-35), which would uncover portions of the substrate that are not part of the pattern.

With respect to claim 57, Guire et al. teach providing a master array having a support surface, immobilizing a first set of molecules comprising a plurality of oligonucleotides on the master array support surface to form a pattern of oligonucleotides, hybridizing a second set of molecules comprising multi-ligand conjugates with the oligonucleotides on the master array support surface, providing an assay array support surface, and disassociating the first binding domains from the master array support that permits the conjugates to remain upon the assay support surface, such as by altering the temperature, pH, or salt concentration of the system (column 17, line 40 – column 18, line 25, column 6, lines 16-31), Guire et al. further teach that the multi-ligand conjugates comprise a recognition component comprising an oligonucleotide binding domain selected to bind to the first set of molecules, and a reactive functional group comprising a ligand such as acrylic or vinyl groups in order to bind to an assay array support via attachment sites (column 3, lines 25-45). Guire et al. do not clearly establish that the step of altering the temperature involves heating, or that the multi-ligand conjugates directly forms a bond with a surface of the second substrate.

Pellicciari et al., however, teaches that DNA in solution is denatured under high temperatures (p.214, lines 3-25). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have altered the temperature in the method of Guire et al. by heating, as suggested by Pellicciari et al., so that the oligonucleotides could be denatured.

Liang et al. further teach a means for immobilizing nucleic acids, and more specifically teach that silane-nucleic acid conjugates can be constructed and reacted with a glass surface at

similar efficiencies as normal silane and that this allows for conjugation and glass immobilization reactions to be accomplished in the shortest time, while incurring minimal background signals (para. 0015). Liang et al. further teach that this allows nucleic acids to be attached directly onto untreated glass and silicon surfaces (para. 0004). Furthermore, Miyamoto et al. disclose that bond between the Si in a silane molecule and a glass substrate is strengthened by heating, and therefore, the heating step for breaking the bonds between the DNA molecules would strengthen the bond between the silane and the glass substrate.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have had used functional groups such as thiols as the ligand for immobilizing the multi-ligand conjugates of Guire et al. on the surfaces of assay array supports, which are comprised of glass or silicon, as Liang et al. teach that this would allow for conjugation and glass immobilization reactions of the multi-ligands of Guire et al. to be accomplished in a short amount of time, while producing immobilized ligands that would incur minimal background signals. Furthermore, one of ordinary skill in the art at the time of the invention would have found it advantageous to utilize the conjugates of Liang et al. as this would allow the conjugates to be immobilized directly on untreated glass or silicon, thus simplifying the method of Guire et al. by avoiding the need for attachment sites.

One of ordinary skill in the art at the time of the invention would also have been motivated to utilize the conjugates of Liang et al., as the application of heat to disassociate the DNA of Guire et al. would strengthen the siloxane bonds between the silane and the substrate. Furthermore since the multi-ligand conjugates of Guire et al. are directed toward immobilization on a support, and since the ligands of Liang et al. are also directed toward immobilization on a

support, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in substituting the conjugates of Liang et al. further multi-ligand conjugates of Guire et al.

It is noted that the optional steps recited have not been considered, as they are not recited as being optional for the method and therefore the claims would encompass a method which did not include the steps

15. With respect to claim 106, Guire et al. teach an embodiment where portions of the second substrate are free of the multi-ligand components (see fig. 1A). Therefore, since the pattern on the third substrate is formed by the same process as the second, portions of the third substrate would also be free of molecules.

16. With respect to claims 107, 109, Guire et al. teach that the assay arrays may then be used as master arrays to form corresponding assays arrays by the same process (column 18, lines 55-63). Guire et al. teach passivating the surface of the assay array prior to and/or after exposure to the binding partner, such as with a surfactant (column 17, lines 1-5) or using wet chemical etching procedures to etch the substrate (column 21, lines 70-11). Guire et al. further teach washing excess conjugates from the surface of the substrate (column 21, liens 30-35), which would uncover portions of the substrate that are not part of the pattern.

With respect to claims 246-247, Guire et al. teach providing a master array having a support surface, immobilizing a first set of molecules comprising a plurality of oligonucleotides on the master array support surface to form a pattern of oligonucleotides, hybridizing a second set of molecules comprising multi-ligand conjugates with the oligonucleotides on the master array support surface, providing an assay array support surface, and disassociating the first

binding domains from the master array support that permits the conjugates to remain upon the assay support surface, such as by altering the temperature, pH, or salt concentration of the system (column 17, line 40 – column 18, line 25, column 6, lines 16-31), Guire et al. further teach that the multi-ligand conjugates comprise a recognition component comprising an oligonucleotide binding domain selected to bind to the first set of molecules, and a reactive functional group comprising a ligand such as acrylic or vinyl groups in order to bind to an assay array support via attachment sites (column 3, lines 25-45). Guire et al. do not clearly establish that the step of altering the temperature involves heating, or that the multi-ligand conjugates directly forms a bond with a surface of the second substrate.

Pellicciari et al., however, teaches that DNA in solution is denatured under high temperatures (p.214, lines 3-25). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have altered the temperature in the method of Guire et al. by heating, as suggested by Pellicciari et al., so that the oligonucleotides could be denatured.

Liang et al. further teach a means for immobilizing nucleic acids, and more specifically teach that silane-nucleic acid conjugates can be constructed and reacted with a glass surface at similar efficiencies as normal silane and that this allows for conjugation and glass immobilization reactions to be accomplished in the shortest time, while incurring minimal background signals (para. 0015). Liang et al. further teach that this allows nucleic acids to be attached directly onto untreated glass and silicon surfaces (para. 0004). Furthermore, Miyamoto et al. disclose that bond between the Si in a silane molecule and a glass substrate is strengthened by heating, and therefore, the heating step for breaking the bonds between the DNA molecules would strengthen the bond between the silane and the glass substrate.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have had used functional groups such as thiols as the ligand for immobilizing the multi-ligand conjugates of Guire et al. on the surfaces of assay array supports, which are comprised of glass or silicon, as Liang et al. teach that this would allow for conjugation and glass immobilization reactions of the multi-ligands of Guire et al. to be accomplished in a short amount of time, while producing immobilized ligands that would incur minimal background signals. Furthermore, one of ordinary skill in the art at the time of the invention would have found it advantageous to utilize the conjugates of Liang et al. as this would allow the conjugates to be immobilized directly on untreated glass or silicon, thus simplifying the method of Guire et al. by avoiding the need for attachment sites.

One of ordinary skill in the art at the time of the invention would also have been motivated to utilize the conjugates of Liang et al., as the application of heat to disassociate the DNA of Guire et al. would strengthen the siloxane bonds between the silane and the substrate. Furthermore since the multi-ligand conjugates of Guire et al. are directed toward immobilization on a support, and since the ligands of Liang et al. are also directed toward immobilization on a support, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in substituting the conjugates of Liang et al. further multi-ligand conjugates of Guire et al.

It is noted that the optional steps recited have not been considered, as they are not recited as being optional for the method and therefore the claims would encompass a method which did not include the steps

17. Claims 40 and 97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guire et al. [US 6,514,768] in view of Liang et al. [US 2003/0148304], as applied to claim 1 above, and further in view of Aksay et al. [US 2001/0023024].

With respect to claims 40, 97, Guire et al. teach providing a master array having a support surface that may be metal (column 7, lines 53-58) to form a pattern (column 3, lines 60-65), immobilizing a plurality of oligonucleotides on the master array support surface, hybridizing multi-ligand conjugates with the oligonucleotides on the master array support surface, providing an assay array support surface, and disassociating the first binding domains from the master array support that permits the conjugates to remain upon the assay support surface (, such as by altering the temperature, pH, or salt concentration of the system (column 17, line 40 – column 18, line 25, column 6, lines 16-31), which one of ordinary skill in the art at the time of the invention would know would encompass heating, as evidenced by Pellicciari et al., who teaches that DNA in solution can be denatured in high temperatures (p.214, lines 3-25). Guire et al. fail to teach that the patterning is performed using electron beam lithography on a metal surface.

Aksay et al. teach using electron beam lithography to form patterns on arrays (para. 0080) and further teach that this allow for thinner structures to be formed.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have used electron beam lithography to form the patterns in the master array of Guire et al., as suggested by Aksay et al., in order to form small patterns, thus decreasing the size of the array formed.

Allowable Subject Matter

18. The following is a statement of reasons for the indication of allowable subject matter: the species of breaking the attractive force or bonds between the first set of molecules and the second set of molecules by using a solution having a high ionic strength would be novel because although Guire et al. teach denaturing the nucleic acids in order to disassociate the strands, this would only be accomplished in solutions having a low ionic strength. Therefore, applying a solution with a high ionic strength would teach away from the denaturing the nucleic acids of Guire et al., as evidenced by Pellicciari et al. [Pellicciari et al., Methods of denaturation and renaturation of DNA in interphasic chromatin: cytochemical quantitative analysis by methyl green staining, 1978, Histochem Journal, 10: pp.213-222] (see p. 214, lines 3-20).

Response to Arguments

19. Applicant's arguments with respect to claims 1, 40, 49-50, 52, 57, 97, 106-107, 109, 246, and 247 have been considered but are moot in view of the new ground(s) of rejection.

In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, as discussed above, Liang et al. teach that silane-nucleic acid conjugates can be constructed and reacted with a glass surface at similar efficiencies as normal

silane, and that this allows for conjugation and glass immobilization reactions to be accomplished in the shortest time, while incurring minimal background signals (para. 0015).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have had used functional groups such as thiols as the ligand for immobilizing the multi-ligand conjugates of Guire et al. on the surfaces of assay array supports, which are comprised of glass or silicon, as Liang et al. teach that this would allow for conjugation and glass immobilization reactions of the multi-ligands of Guire et al. to be accomplished in the shortest time.

Applicant further argues that Guire et al. requires a linker comprising a binding partner and references several areas of the patent. The Office notes, however, that Guire et al. merely states that the ligand **optionally** comprises a binding ligand adapted to form bonds with a corresponding partner (see column 15, lines 13-30). While Guire et al. discloses that the ligand can be provided in the form of a polymerizable group such as acrylic and vinyl, which can be further polymerized, these are all techniques directed toward immobilizing the multi-ligand conjugates on an assay support surface. Since Liang et al. teach an alternative means for immobilizing conjugates on a support surface, Liang et al. does not teach away from the invention.

Nor does Guire et al. require that the assay support surface be pretreated with a binding ligand. While Guire et al. disclose that "the surface of a discrete assay array support can be pretreated to facilitate attachment of the oriented conjugate layer" (see column 16, lines 49-51), Guire does not require that the surface of the support be pretreated. Furthermore, the sole purpose of the pretreatment is to facilitate attachment of the conjugate. As discussed in the

previous actions and from this statement, one of ordinary skill in the art at the time of the invention would realize the linkers of Guire et al. are merely utilized to immobilize the ligands, and that Liang simply provides an alternative and more efficient way of immobilizing the ligands.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

20. Therefore, applicant's arguments are not found persuasive.

Conclusion

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nelson Yang whose telephone number is (571)272-0826. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on (571)272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

22. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nelson Yang/
Primary Examiner, Art Unit 1641